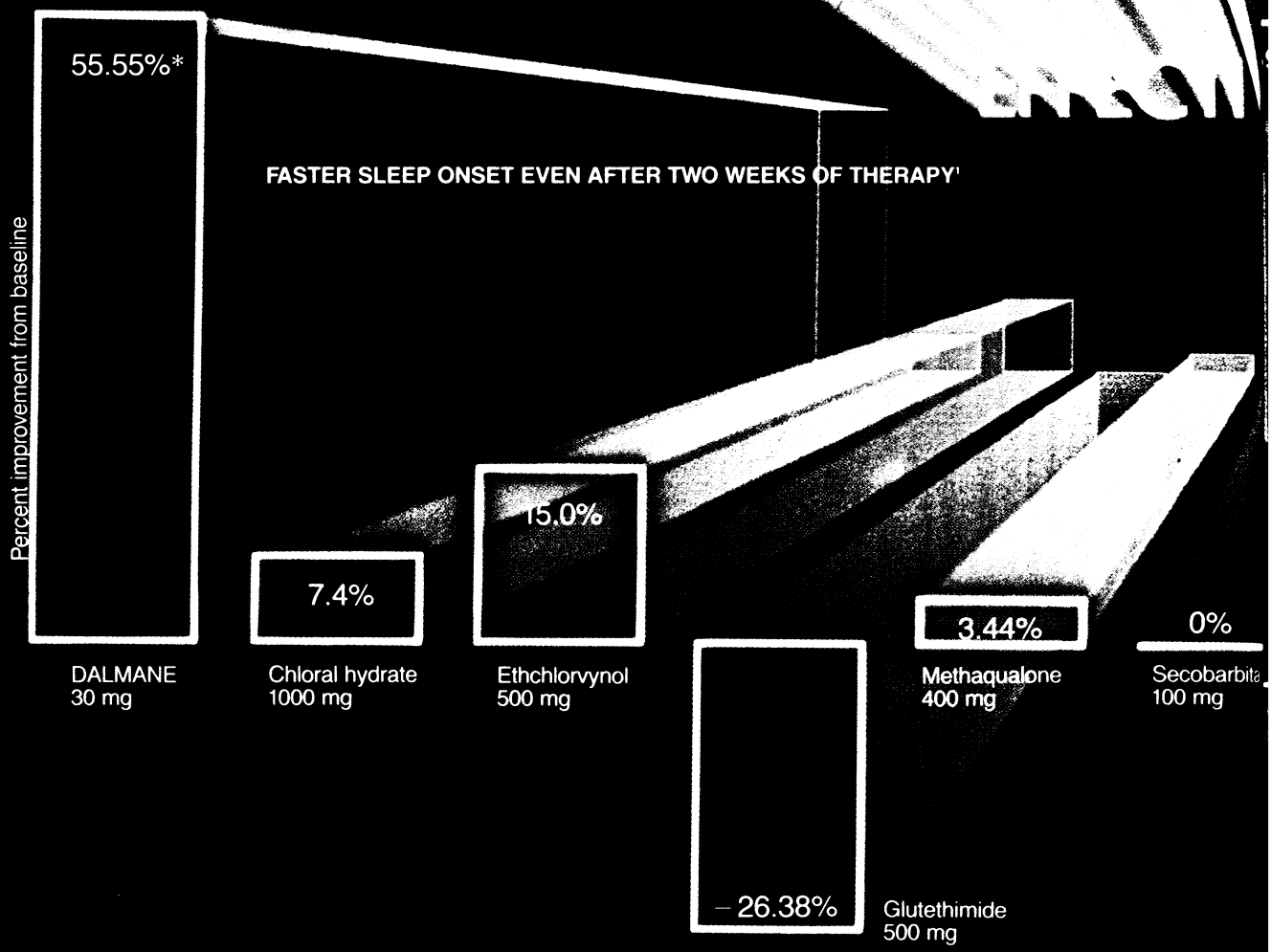
EFFECTIVE



THE MOST INTENSIVELY STUDIED SLEEP MEDICATION

Efficacy of Dalmane (flurazepam HCl/Roche) has been documented in 9141 insomniac patients evaluated in 185 clinical studies. In addition, Dalmane efficacy has been proven in the sleep research laboratory during 995 subject nights.[2]

WITH AN UNSURPASSED RECORD OF SAFETY

In a study of 2542 hospitalized medical patients with insomnia, adverse reactions were reported in only 3.1% or 78 patients. These reactions consisted predominantly of unwanted residual drowsiness; none were considered serious by attending physicians.[3] Safety has also been demonstrated by lack of interference with many commonly ordered laboratory tests [4,5] and no unacceptable fluctuation in prothrombin time in patients on chronic warfarin therapy.[6,7]

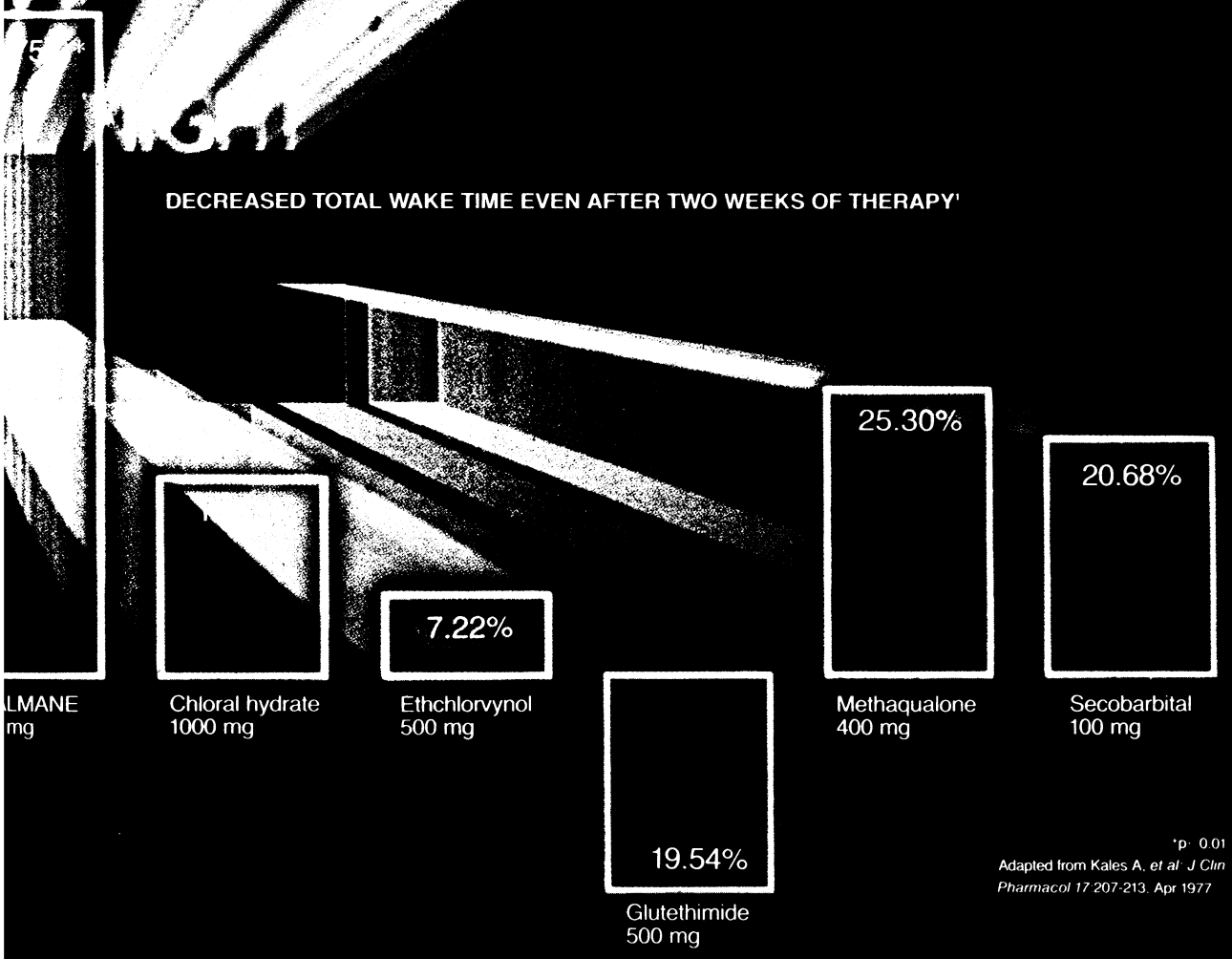
AND SLEEP WITHIN 17 MIN NO WORSENING OF SLEEP ON DISCONTINUAT

Rapid sleep induction, within 1 minutes on average,[3] sets the for insomnia relief, with improv ment that continues.

In reviewing the experience discontinuation of Dalmane (flurazepam HCl Roche) for pe ranging up to 14 nights, no wo ing of sleep compared with ba was observed.[4]

Should insomnia recur, the p may require guidance in settin regular sleep program to help

ALL NIGHT



†p< 0.01
Adapted from Kales A. *et al. J Clin Pharmacol* 17:207-213. Apr 1977

ne optimum environment for
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rapy is required, it should be
for the shortest time at the
t effective dose to achieve the
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ients receiving Dalmane
zepam HCl/Roche) should be
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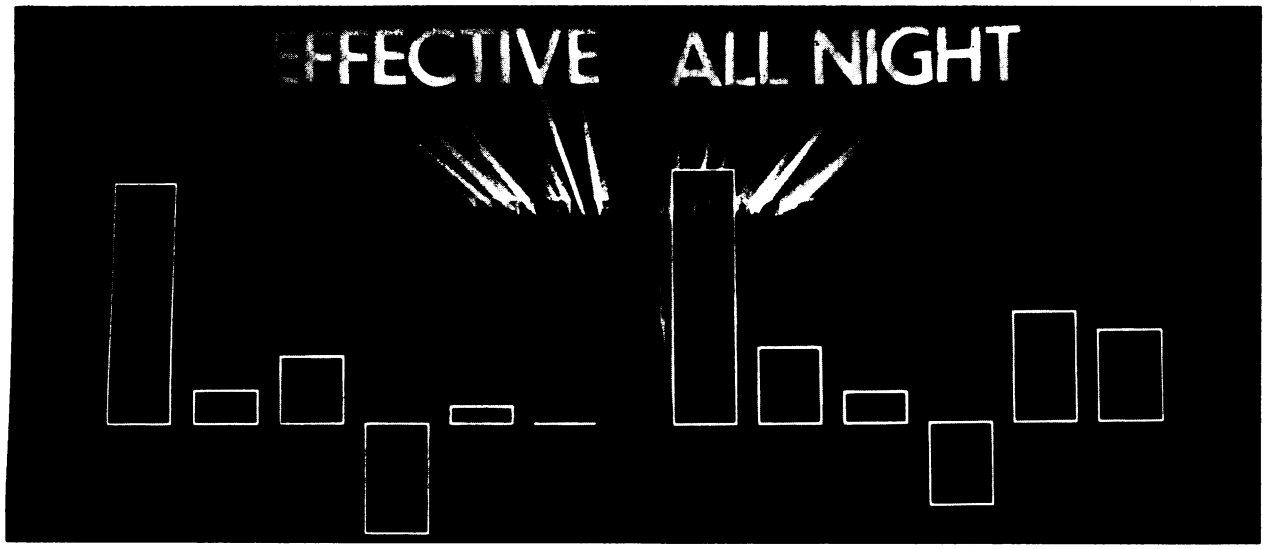
g in hazardous occupations
ing complete mental alertness
as operating machinery or
g a motor vehicle after ingesting
rug.

DALMANE® (IV)
flurazepam HCl/Roche

THE STANDARD OF HYPNOTIC EFFICACY FROM THE LEADER IN SLEEP RESEARCH

ROCHE®

Please see following page for a summary of product information.



SLEEP-SPECIFIC
DALMANE® (IV)
flurazepam HCl/Roche

One 15-mg capsule *h.s.*–recommended initial dosage for elderly or debilitated patients.
One 30-mg capsule *h.s.*–usual adult dosage
(15 mg may suffice in some patients).

THE STANDARD FOR HYPNOTIC EFFICACY WITH IMPORTANT ADDED BENEFITS

- Well tolerated[2]
- No chemical interference with many commonly ordered laboratory tests, including triglycerides, uric acid, glucose, SGOT, alkaline phosphatase and total protein[4,5] (See adverse reactions section of complete product information.)
- Compatible with chronic warfarin therapy; no unacceptable fluctuation in prothrombin time reported[6,7]

UNLIKE NONSPECIFIC MEDICATIONS USED FOR SLEEP

Tricyclic antidepressants

–which are *not* sleep specific,[9] yet are sometimes used in nondepressed patients for sleep

–which can cause transient insomnia in the elderly[10]

–which can require careful monitoring in cardiovascular patients[10]

–which have strong anticholinergic effects[10]

Antihistamines

–which are *not* reliable sleep-inducing agents[11]

–which may produce stimulation instead[11]

–which have anticholinergic effects[11]

Major tranquilizers

–whose side effects may be troublesome for nonpsychotic patients[12]

–where tolerance for sedation appears rapidly[12]

Dalmane does not cause significant worsening of sleep beyond baseline levels upon discontinuation.[8]

References: 1. Kales A, *et al: J Clin Pharmacol 17*:207-213, Apr 1977 **2.** Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ **3.** Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther 21*:355-361, Mar 1977 **4.** Moore JD, Weissman L: *J Clin Pharmacol 16*:241-244, May-Jun 1976 **5.** Spiegel HE: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ **6.** Robinson DS, Amidon EL: Interaction of benzodiazepines with warfarin in man, in *The Benzodiazepines*, edited by Garattini S, Mussini E, Randall LO. New York, Raven Press, 1973, pp. 641-646 **7.** Warfarin Study: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ **8.** Kales A, *et al: Clin Pharmacol Ther 18*:356-363, Sep 1975 **9.** Baldessarini RJ: Drugs and the treatment of psychiatric disorders, chap. 19, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, ed 6. New York, Macmillan Publishing Co. Inc., 1980, pp. 391-447 **10.** Cole JO, Davis JM: Antidepressant drugs, chap. 31.2, in *Comprehensive Textbook of Psychiatry/II*, edited by Freedman AM, Kaplan HI, Sadock BJ, ed 2. Baltimore, The Williams & Wilkins Company, vol 2, 1976, pp. 1941-1956 **11.** Douglas WW: Histamine and 5-hydroxytryptamine (serotonin) and their antagonists, chap. 26, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, ed 6. New York, Macmillan Publishing Co. Inc., 1980, pp. 609-646 **12.** Davis JM, Cole JO: Antipsychotic drugs, chap. 31.1, in *Comprehensive Textbook of Psychiatry/II*, edited by Freedman AM, Kaplan HI, Sadock BJ, ed 2. Baltimore, The Williams & Wilkins Company, vol 2, 1976, pp. 1921-1940

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended. Repeated therapy should only be undertaken with appropriate patient evaluation.

Contraindications: Known hypersensitivity to flurazepam HCl; pregnancy. Benzodiazepines may cause fetal damage when administered during pregnancy. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.

Dosage: Individualize for maximum beneficial effect.
Adults: 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients*: 15 mg recommended initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

ROCHE®
ROCHE PRODUCTS INC.
Manati, Puerto Rico 00701

An added complication... in the treatment of bacterial bronchitis*

Brief Summary.
Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae,* and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Precautions: If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coomb testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Usage in Pregnancy—Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus.

Usage in Infancy—Safety of this product for use in infants less than one month of age has not been established.

Adverse Reactions: Adverse effects considered related to cefaclor therapy are uncommon and are listed below:

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70) and nausea and vomiting (1 in 90).

As with other broad-spectrum antibiotics, colitis, including rare instances of pseudomembranous colitis, has been reported in conjunction with therapy with Ceclor.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor® (cefaclor). Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200). [100281R]

*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.[5]

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

References

1. Antimicrob. Agents Chemother., *8*:91, 1975.
2. Antimicrob. Agents Chemother., *11*:470, 1977.
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5. Current Chemotherapy (edited by W. Siegenthaler and R. Luthy), II:880. Washington, D.C.: American Society for Microbiology, 1978.
6. Antimicrob. Agents Chemother., *13*:861, 1978.
7. Data on file, Eli Lilly and Company.
8. Principles and Practice of Infectious Diseases (edited by G.L. Mandell, R.G. Douglas, Jr., and J.E. Bennett), p. 487. New York: John Wiley & Sons, 1979.

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285.

Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630

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Break the habit of paying your malpractice insurance premiums

CAP/MPT now offers affordable pro[illegible] for all risk-specia[illegible]

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[illegible]RN CALIFORNIA OFFICE: 50[illegible]
ORANGE COUNTY OFFICE: [illegible]

ENTERO-TEST,® A 140cm nylon line coiled inside of a gelatin capsule designed to retrieve duodenal contents without intubation. Easily administered and tolerated. ENTERO-TEST® has the following advantages:

- A viable alternative to intubation
- Well tolerated by all age groups
- Pediatric sizes available
- Useful in the diagnosis of bleeding and a variety of intestinal parasites

Rosenthal and Leibman studied 23 pediatric patients with diarrhea. All had one or more negative stools. Of these, 5 patients had *Giardia lamblia* which was diagnosed by the simple ENTERO-TEST® procedure. Lopez and co-workers diagnosed Giardiasis in 22 patients with the ENTERO-TEST® compared to 4 patients by stool exams. ENTERO-TEST® has proved to be a useful and effective method for the localization of upper GI bleeding, and the diagnosis of Typhoid carriers, strongyloidiasis and other parasitic diseases.

References:

Rosenthal, P., and Liebman, W.M: Comparative study of stool examinations, duodenal aspiration and pediatric Entero-Test for giardiasis in children. *J. PEDIAT. 96:* 278 (Feb.) 1980.

Thomas, G. E., et al: Use of the Entero-Test duodenal capsule in the diagnosis of giardiasis. *South Afr. Med J. 48:* 2219, 1974.

Lopez, M. E., et al: Infeccion duodeno-yeyunal en el niño con desnutricion energetico-proteinica. *Rev. Med. Hosp. Nat. Niños 13:* 53, 1978.

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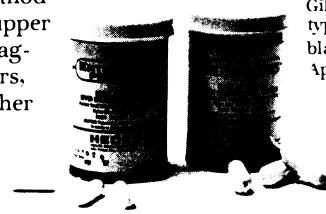

ENTERO-TEST,® The Solution. Simple And Convenient.

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Mountain View
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Only one beta-blocker provides once-a-day round-the-clock protection in both hypertension and angina pectoris.

CORGARD®
[nadolol tablets]
IS THE ONE

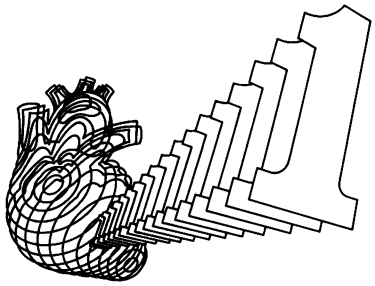
Reliable 24-hour beta blockade at all titrated dosages

SQUIBB®

Innovators in cardiovascular medicine

See next page for brief summary.

The only once-a-day beta-blocker for both hypertension and angina pectoris



CORGARD®
nadolol tablets
40 mg, 80 mg, 120 mg, 160 mg scored tablets

CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic p tial was seen in any of these species. There are no well-controlled studies in pregn women; therefore, use nadolol in pregnant women only if potential benefit justifi potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. B many drugs are excreted in human milk, exercise caution when nadolol is administe nursing woman. Animal studies showed that nadolol is found in the milk of lactati

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute commonly, and heart rates below 40 beats per minute and/or symptomatic brady were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac f hypotension, and rhythm/conduction disturbances have each occurred in about 1 patients. Single instances of first degree and third degree heart block have been re intensification of AV block is a known effect of beta-blockers (see also CONTRA DICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sed and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDIC TIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal disc fort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following report to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impoten decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffine sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, disturbances have been reported. The oculomucocutaneous syndrome associated w practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other be adrenergic blocking agents have not been reported with nadolol, they should be con potential adverse effects of nadolol. **Central Nervous System** — reversible mental d sion progressing to catatonia; visual disturbances; hallucinations; an acute reversibl syndrome characterized by disorientation for time and place; short-term memory l emotional lability with slightly clouded sensorium; decreased performance on neur psychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purp **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory d **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodi In addition to gastric lavage, employ the following measures as appropriate. In det mining duration of corrective therapy, take note of long duration of effect of nad

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no re to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been repo that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (The evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 8 increments at 3 to 7 day intervals until optimum clinical response or pronounced slo of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respon mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 m increments until optimum blood pressure reduction is achieved; usual maintenance d is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package in for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tab The 40 mg and 80 mg tablets are also available in convenience packages containing 4 blister cards of 7 tablets each.

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SPOT-RESISTANT
ORAL CONTRACEPTION
IS HERE!
It's LO/OVRAL 30. And here's how it holds spotting and breakthrough bleeding to a minimum: Hormone balance right from the start...and throughout the cycle. Hormone balance made possible with a very low dose oral contraceptive because of the supportive progestational activity of norgestrel, Wyeth's exclusive progestogen.
Regular withdrawal bleeding, too
despite its low dose. In clinical trials amenorrhea—defined as absence of bleeding in the 7 pill-free days—was reported in only 2.1% of total cycles. And when defined as absence of bleeding for 60 days or more (as it often is), the incidence was only 0.2%.*
And comfort for most patients*
thanks to the same balance that helps prevent spotting and breakthrough bleeding. In the clinical trials, most patients stayed free of common side effects such as nausea (0.6% of cycles), vomiting (0.1%), depression (0.5%) and acne (0.9%).
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LO OVRAL—1st cycle

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Even in the first cycle, the effective action of LO OVRAL on the endometrium, such as you see here, provides the resistance against spotting and breakthrough bleeding you hope to achieve.

HISTOLOGICALLY... AND CLINICALLY.

4.2% SPOTTING

2.9% BREAKTHROUGH BLEEDING

[illegible]

A near-spotless record— in clinical trials involving 22,489 cycles*

[illegible]

See full prescribing information

LO/OVRAL 30 mcg

[illegible]

...with a near-spotless record!

See important information on following page

IN BRIEF:

Indications and Usage—LO/OVRAL® is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception.

Contraindications—OC's should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep-vein thrombophlebitis or thromboembolic disorders.
3. Cerebral-vascular or coronary-artery disease.
4. Known or suspected carcinoma of the breast.
5. Known or suspected estrogen-dependent neoplasia.
6. Undiagnosed abnormal genital bleeding. 7. Known or suspected pregnancy (see Warning No. 5). 8. Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products.

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exists, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users.

If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy; Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's; clinical significance of this finding remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mi In undiagnosed persistent or recurrent abnormal bleeding fro the vagina, adequate diagnostic measures are indicated to ru out pregnancy or malignancy. If pathology has been excluded time or change to another OC may solve the problem. Changi to an OC with a higher estrogen content, while potentially use in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembo disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycle may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previou irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effect if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatmen and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should not be prescribed for longer tha 1 year without another physical examination.

2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternati method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, t patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy ha an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients wi impaired liver function and should be administered with caution

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling.

Drug Interactions—Reduced efficacy and increased incidence breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin an tetracycline.

Carcinogenesis—See Warnings on carcinogenic potential of O

Pregnancy—Category X. See Contraindications, Warnings.

Nursing Mothers—See Warnings.

Adverse Reactions—An increased risk of these serious adver reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies. There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related. Nausea and/or vomiting, usually the most common adverse reactions, occur approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (su as abdominal cramps and bloating); breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, amenorrhe during and after treatment, temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist; breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); chang in cervical erosion and cervical secretion; possible diminution l lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata. rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvatur (steepening), intolerance to contact lenses.

The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hai erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

LO/OVRAL® each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol

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Why you should buy your medical computer system from a specialist instead of a general practitioner.

At Westland Medical Systems we do not try to be all things to all people.

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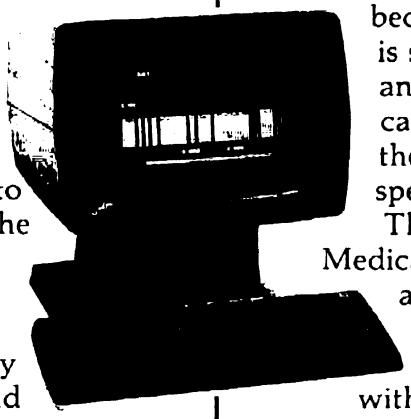

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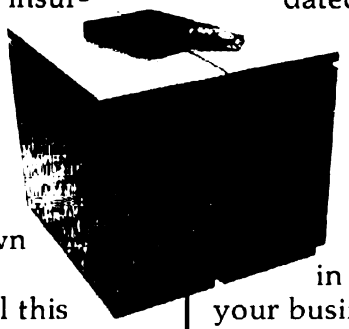

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Your System can be set up and your people trained, in a matter of days. Best of all, this can be accomplished without interfering with the course of your work.

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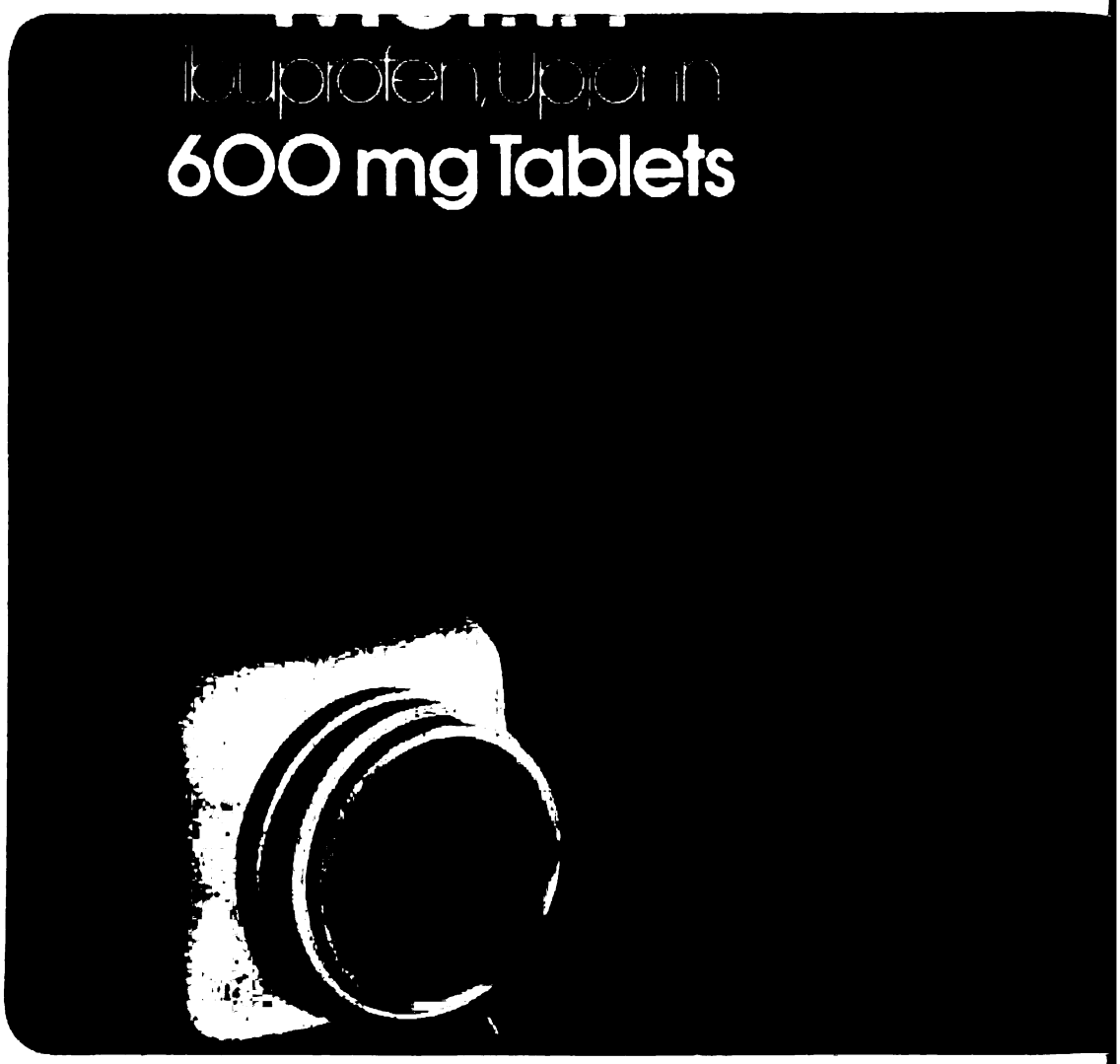


***For moderate to severe vasomotor symptoms, atrophic vaginitis, surgical menopause, postmenopausal osteoporosis†**

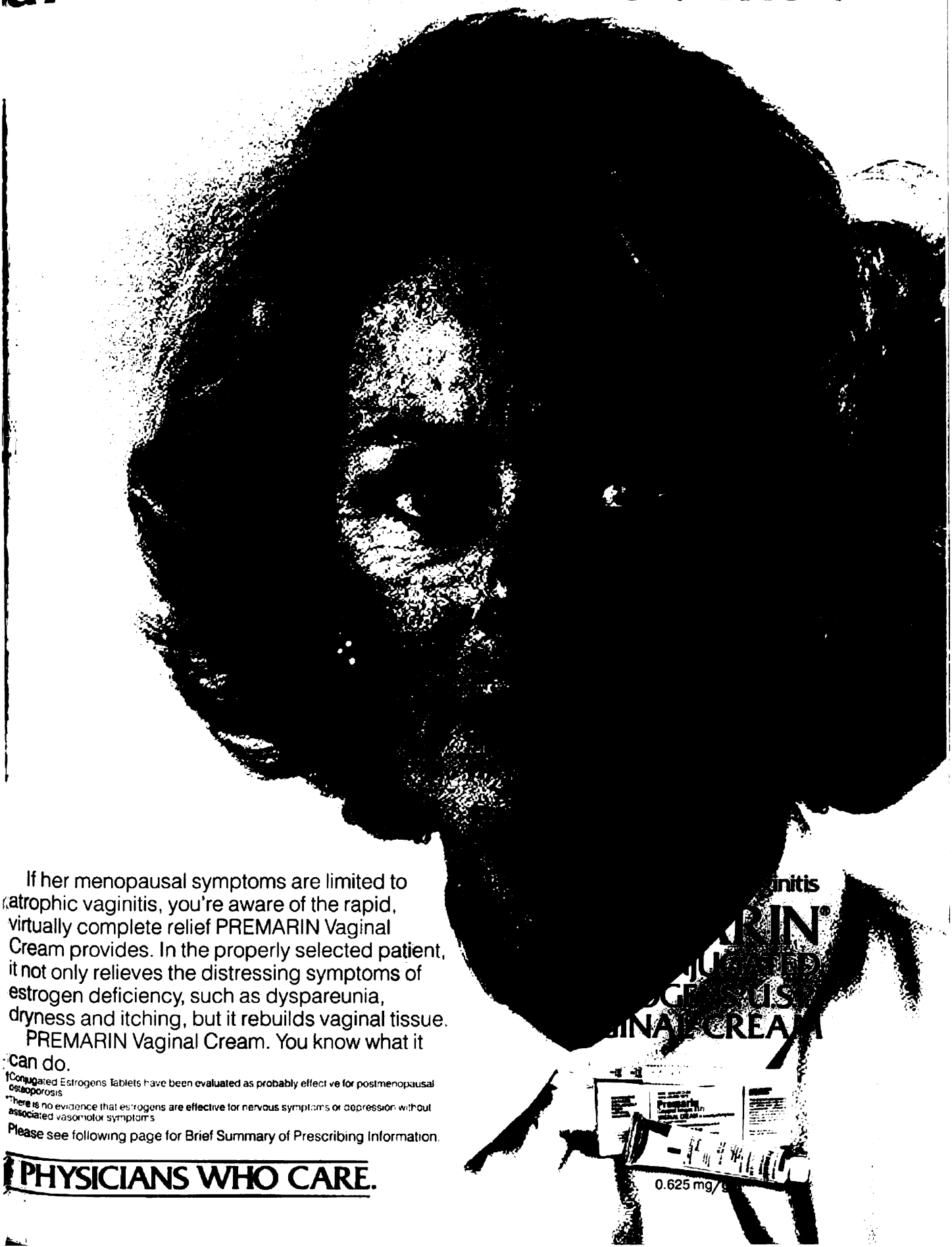
PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

Counseling. It can help the menopausal woman through this difficult time. But counseli can't stop the moderate to severe vasomotor symptoms, reverse vaginal atrophy, or retard postmenopausal osteoporosis† the way PREMARIN tablets can.

PREMARIN. It may slow the progression of osteoporosis.† It controls her embarrassing sweats and hot flushes. Relieves her discomf Helps her cope.** PREMARIN is a useful adjunct in your expert management of her menopausal symptoms.

PRESCRIBED WITH CA

UT PREMARIN® HELPS HER CONDITION*



If her menopausal symptoms are limited to atrophic vaginitis, you're aware of the rapid, virtually complete relief PREMARIN Vaginal Cream provides. In the properly selected patient, it not only relieves the distressing symptoms of estrogen deficiency, such as dyspareunia, dryness and itching, but it rebuilds vaginal tissue.

PREMARIN Vaginal Cream. You know what it can do.

†Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis

*There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms

Please see following page for Brief Summary of Prescribing Information.

PHYSICIANS WHO CARE.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA
Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population based cancer report-ng systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in non-users. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.
2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.
The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences – National Research Council and/or other information, FDA has classified the indications for use as follows
Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)
2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma – palliative therapy of advanced disease
9. Postpartum breast engorgement – Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.
PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING)
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning) 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time, there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.
Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day, comparable to those used to treat cancer of the prostate and breast) have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. With doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.
Benign hepatic adenomas should be considered in estrogen users having abdominal pain, tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormally excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, and in young patients in whom bone growth is not complete.
The following changes may be expected with larger doses of estrogen:
a. Increased sulfobromophthalein retention.
b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.
d. Impaired glucose tolerance.
e. Decreased pregnanediol excretion.
f. Reduced response to metyrapone test.
g. Reduced serum folate concentration.
h. Increased serum triglyceride and phospholipid concentration.
As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary, since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, premenstrual-like syndrome, amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis; change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression; chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.
ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:
PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.
1. *Given cyclically for short-term use only.* For treatment of moderate to severe vasomotor symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.2 mg or more daily).
The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.
Administration should be cyclic (e.g., three weeks on and one week off).
Attempts to discontinue or taper medication should be made at three to six month intervals.
2. *Given cyclically.* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.
Female hypogonadism – 2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.
If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.
Female castration and primary ovarian failure – 1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.
Osteoporosis (to retard progression) – 1.25 mg daily cyclically.
3. *Given for a few days.* Prevention of postpartum breast engorgement – 3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.
4. *Given chronically.* Inoperable progressing prostatic cancer – 1.25 to 2.5 mg three times daily.
Inoperable progressing breast cancer in appropriately selected men and postmenopausal women – 10 mg three times daily for a period of at least three months.
Patients with an intact uterus should be monitored for signs of endometrial cancer; appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream
Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.
The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.
Administration should be cyclic (e.g., three weeks on and one week off).
Attempts to discontinue or taper medication should be made at three to six month intervals.
Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.
Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens) Tablets, U.S.P.) No. 865 – Each *pink* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866 – Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 867 – Each *red* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 868 – Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.
PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream – No. 872 – Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white petrolatum, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)
Combination package. Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.
Also Available. Refill package. Each contains Net Wt. 1½ oz. (42.5 g) tube. 7814

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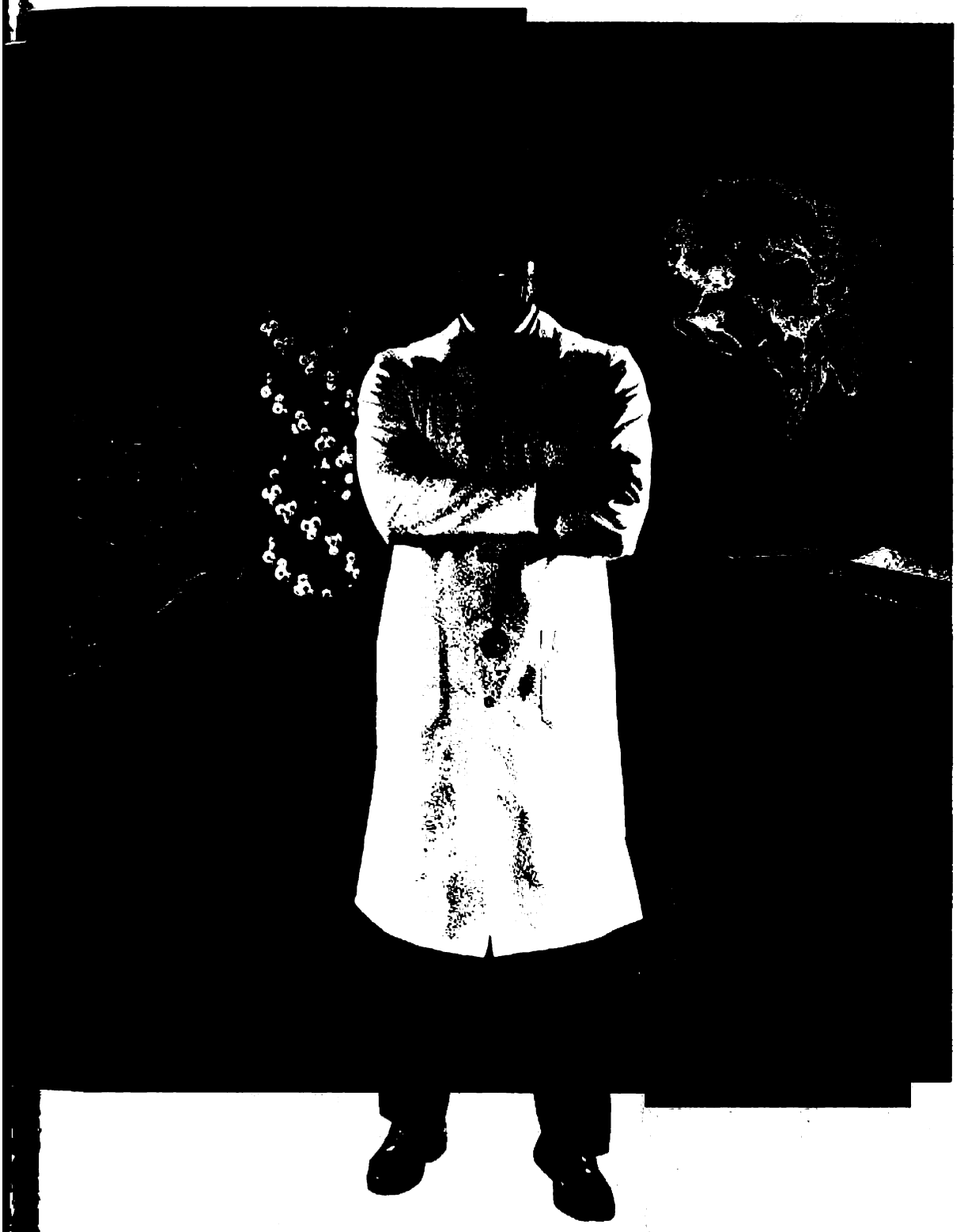
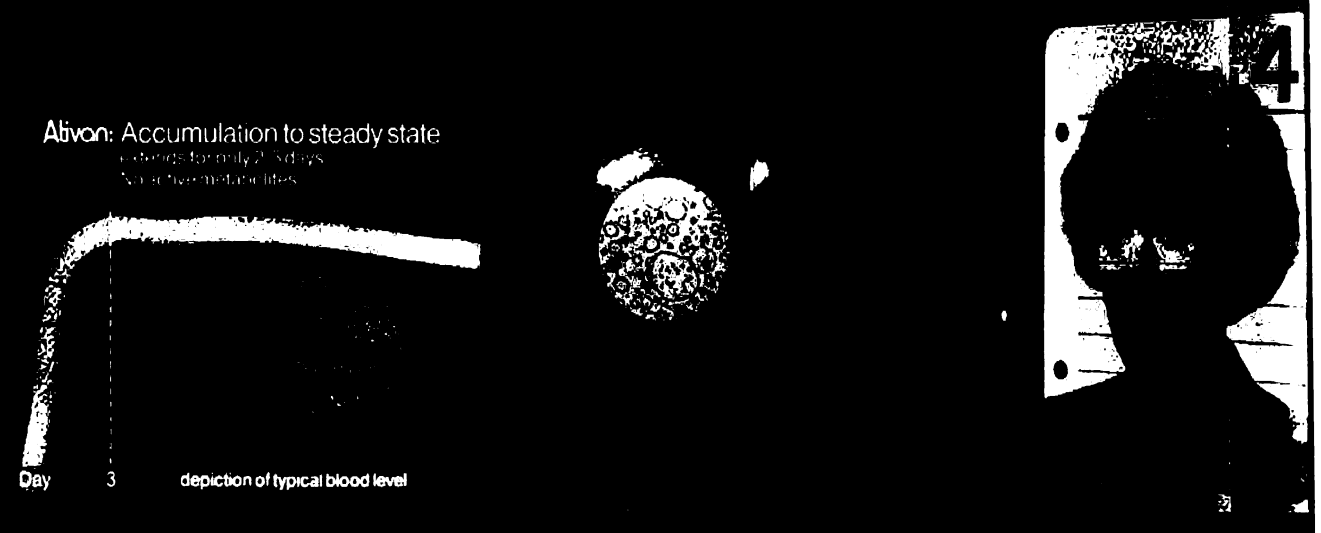


Ativan®: Agent of C
lorazepam)



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it doesn't interact with drugs metabolized by P450 microsomal enzymes

Most benzodiazepines undergo oxidative metabolism and thus utilize the hepatic microsomal enzyme system. Ativan® (lorazepam), however, is metabolized by glucuronidation and does not compete with other drugs for cytochrome P450. Thus, when Ativan is given with Tagamet® (cimetidine), for example, clearance is not delayed, nor sedation increased†—unlike reported observations with patients on other benzodiazepines.[1-5]

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rmacokinetics cannot as yet be directly related to efficacy
enzodiazepines produce additive effects when given with CNS ressants such as barbiturates or alcohol

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- Little accumulation lessens likelihood of excessive sedation
- Unlike most benzodiazepines, Ativan does not compete with other drugs, such as Tagamet® (cimetidine), for microsomal enzyme system during biotransformation
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- Promptly eliminated from patient's system after discontinuation
- Specifically evaluated and found effective for anxiety associated with cardiovascular and gastrointestinal disorders
- A distinctive change from long-acting benzodiazepines, all of which have active metabolites and are much the same

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. Studies in humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decrease of dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.4%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

***Dosage:* Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose by increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d.-t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. In elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

***How Supplied:* 0.5, 1.0 and 2.0mg tablets.**

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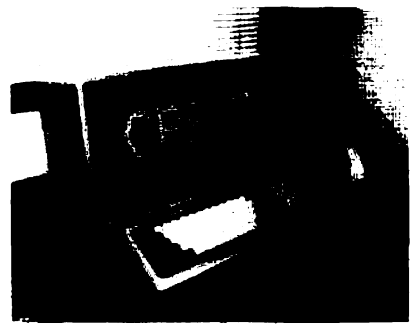

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(Continued on Page 28)

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References
1. Wolf R, Pretschner P, Engels HJ, Hundeshagen H, Lichtlen PR: The effect of isosorbide dinitrate on stress-induced abnormal myocardial perfusion in coronary disease, substantiated by 201-thallium scintigraphy. *Zeitschrift für Kardiologie* 68:676-686, 1979.
2. Data on file, Ives Laboratories.

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

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Contraindication: Idiosyncrasy to this drug.
Warnings: Data supporting the use of nitrites and nitrates during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.
Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur. In patients with functional or organic gastrointestinal hypermotility or malabsorption syndrome, it is suggested that oral Titradose tablets, sublingual or chewable tablets, or Tembids **capsules** be the preferred therapy because a few patients have reported passing partially dissolved Tembids **tablets** in their stools. This phenomenon is believed to be on the basis of physiologic variability and to reflect rapid gastrointestinal transit of the tablet.
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(Continued from Page 26)

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RIMSO®-50
(dimethyl sulfoxide)
50% w/w aqueous solution

INDICATIONS AND USAGE

RIMSO® - 50 (dimethyl sulfoxide) is indicated for the symptomatic relief of patients with interstitial cystitis. RIMSO ® - 50 has not been approved as being safe and effective for any other indication. There is no clinical evidence of effectiveness of dimethyl sulfoxide in the treatment of bacterial infections of the urinary tract.

CONTRAINDICATIONS

None known.

WARNINGS

Dimethyl sulfoxide can initiate the liberation of histamine and there has been occasional hypersensitivity reaction with topical administration of dimethyl sulfoxide. This hypersensitivity has been reported in one patient receiving intravesical RIMSO® - 50. The physican should be cognizant of this possibility in prescribing RIMSO® - 50. If anaphylactoid symptoms develop, appropriate therapy should be instituted.

PRECAUTIONS

Changes in the refractive index and lens opacities have been seen in monkeys, dogs and rabbits given high doses of dimethyl sulfoxide chronically. Since lens changes were noted in animals, full eye evaluations, including slit lamp examinations are recommended prior to and periodically during treatment. Approximately every six months patients receiving dimethyl sulfoxide should have a biochemical screening, particularly liver and renal function tests, and complete blood count.

Intravesical instillation of RIMSO® - 50 may be harmful to patients with urinary tract malignancy because of dimethyl sulfoxide-induced vasodilation.

Some data indicate that dimethyl sulfoxide potentiates other concomitantly administered medications.

Pregnancy Category C. Dimethyl sulfoxide caused teratogenic responses in hamsters, rats and mice when administered intraperitoneally at high doses (2.5-12 gm/kg). Oral or topical doses of dimethyl sulfoxide did not cause problems of reproduction in rats, mice and hamsters. Topical doses (5 gm/kg first two days, then 2.5 gm/kg - last eight days) produced terata in rabbits, but in another study, topical doses of 1.1 gm/kg days 3 through 16 of gestation failed to produce any abnormalities. There are no adequate and well controlled studies in pregnant women. Dimethyl sulfoxide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dimethyl sulfoxide is administered to a nursing woman.

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

A garlic-like taste may be noted by the patient within a few minutes after instillation of RIMSO® - 50 (dimethyl sulfoxide). This taste may last several hours and because of the presence of metabolites, an odor on the breath and skin may remain for 72 hours.

Transient chemical cystitis has been noted following instillation of dimethyl sulfoxide.

The patient may experience moderately severe discomfort on administration. Usually this becomes less prominent with repeated administration.

DOSAGE AND ADMINISTRATION

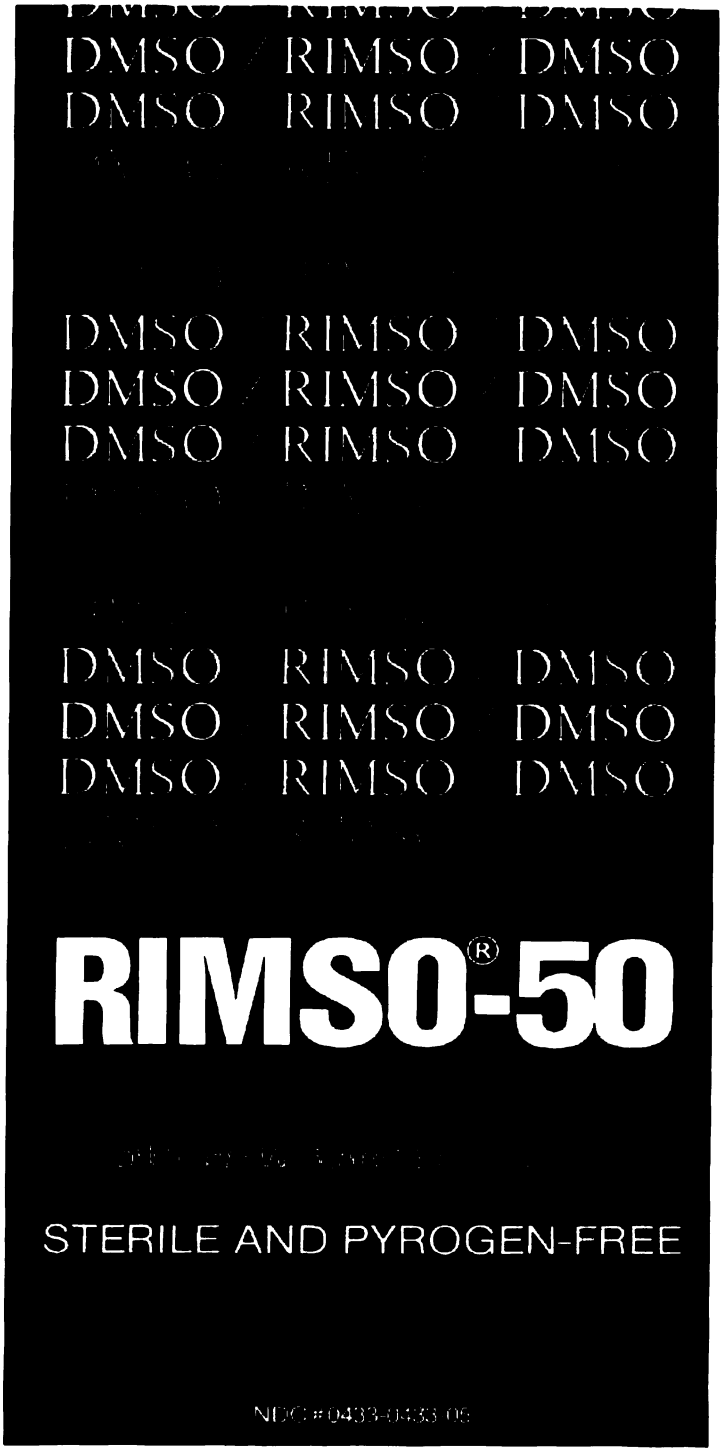
Instillation of 50 ml of RIMSO® - 50 (dimethyl sulfoxide) directly into the bladder may be accomplished by catheter or asepto syringe and allowed to remain for 15 minutes. Application of an analgesic lubricant gel such as lidocaine jelly to the uretha is suggested prior to insertion of the catheter to avoid spasm. The medication is expelled by spontaneous voiding. It is recommended that the treatment be repeated every two weeks until maximum symptomatic relief is obtained. Thereafter, time intervals between therapy may be increased appropriately.

Administration of oral analgesic medication or suppositories containing belladonna and opium prior to the instillation of RIMSO® - 50 can reduce bladder spasm.

In patients with severe interstital cystitis with very sensitive bladders, the initial treatment, and possibly the second and third (depending on patient response) should be done under anesthesia. (Saddle block has been suggested).

HOW SUPPLIED

Bottles contain 50 ml of sterile and pyrogen-free RIMSO® - 50 (50% w/w dimethyl sulfoxide aqueous solution).
Dimethyl sulfoxide is clear and colorless.
Protect from strong light.
Store at room temperature (50° to 86°F) (15° to 30°C).
Do not autoclave.
NDC # 0433-0433-05



FOR FURTHER INFORMATION

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In the treatment of impetigo–

- **100% cure rate with Tegopen®** (cloxacillin sodium)
- **only a 60% cure rate with penicillin V-K**

As seen on admission

After one week of penicillin V-K therapy

Two weeks after initiation of TEGOPEN therapy

Treatment failure was judged to have occurred when lesions increased in size and/or number during the initial week of treatment with penicillin V-K. *No* treatment failures occurred with Tegopen.

*Data on file, Bristol Laboratories.

Brief Summary of Prescribing Information

TEGOPEN®
(cloxacillin sodium)
Capsules and Oral Solution

For complete information, consult Official Package Circular. (12) 9/11/75

INDICATIONS:

Although the principal indication for cloxacillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected. (See Important Note below.)

Bacteriologic studies to determine the causative organisms and their sensitivity to cloxacillin sodium should be performed

IMPORTANT NOTE

When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of cloxacillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semi-synthetic penicillin.

Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

Cloxacillin sodium is a compound that acts through a mechanism similar to that of methicillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross-resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in *in vitro* sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

CONTRAINDICATIONS:

A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication

RESULTS OF ORAL THERAPY revealed a high percentage of treatment failures with penicillin V potassium, but *no* failures with Tegopen.

		Given Tegopen® *(cloxacillin sodium)*	Given *penicillin V-K*
Staphylococcus aureus	(78 patients)	39	39
Returned to clinic at one week		29†	38†
Treatment failure at one week		0	18 (47.4%)
Staphylococcus aureus* and *Streptococcus pyogenes	(9 patients)	4	5
Returned to clinic at one week		4	5
Treatment failure at one week		0	2 (40%)
No initial bacterial growth	(14 patients)	9	5
All 14 healed, regardless of which antibiotic was administered.			
Beta-hemolytic *Streptococcus*	(1 patient)	0	1
TOTALS:	**102 patients**	**52 patients**	**50 patients**

†Eleven patients did not return for their one-week checkup. These were all called by telephone, and their families reported the lesions had healed. One patient was dropped from the study, early, because of adverse reaction to medication.

STUDY: DESCRIPTION/PROTOCOL

- 102 nonselected subjects, with initial bacteriology as follows: 77% *Staphylococcus aureus*, 9% mixed *Staphylococcus aureus* and *Streptococcus pyogenes*, and 1% beta-hemolytic *Streptococcus*.†
- All patients were given randomized therapy—Tegopen capsules or oral solution, or penicillin V-K tablets or oral solution, in recommended dosages according to body weight.
- All patients were evaluated after one week's therapy. If there was no improvement, therapy was switched to the other antibiotic. The "other antibiotic" proved to be Tegopen 100% of the time because no treatment failures had occurred with Tegopen.
- A final assessment of progress was made two weeks after initiation of Tegopen therapy.

†The remainder, to equal 100%, consisted of 14 patients (13%) who exhibited no initial bacterial growth. These 14 were all healed, whether given Tegopen or penicillin V-K.

TEGOPEN®
(cloxacillin sodium)
–effective therapy for staph infections of the skin and skin structures

WARNING:
Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids.

Safety for use in pregnancy has not been established.

PRECAUTIONS:
The possibility of the occurrence of superinfections with mycotic organisms or other pathogens should be kept in mind when using this compound, as with other antibiotics. If superinfection occurs during therapy, appropriate measures should be taken.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy.

ADVERSE REACTIONS:
Gastrointestinal disturbances, such as nausea, epigastric discomfort, flatulence, and loose stools, have been noted by some patients. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Skin rashes and allergic symptoms, including wheezing and sneezing, have occasionally been encountered. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

USUAL DOSAGE:
Adults: 250 mg. q.6h.

Children, 50 mg./Kg./day in equally divided doses q.6h. Children weighing more than 20 Kg. should be given the adult dose. Administer on empty stomach for maximum absorption.

N.B.: INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS.

SUPPLIED:
Capsules—250 mg. in bottles of 100, 500 mg. in bottles of 100.
Oral Solution—125 mg./5 ml. in 100 ml. and 200 ml. bottles.

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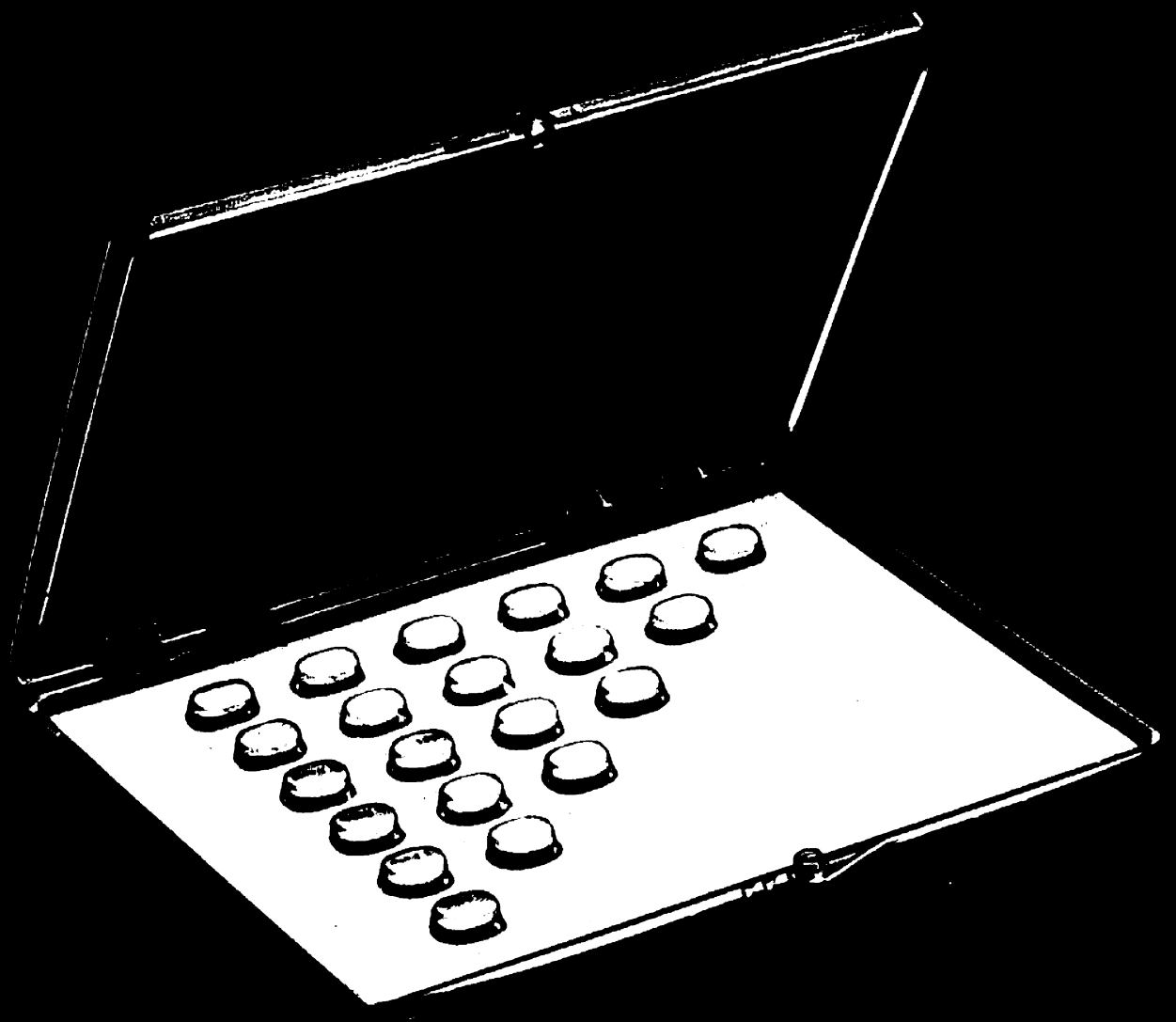

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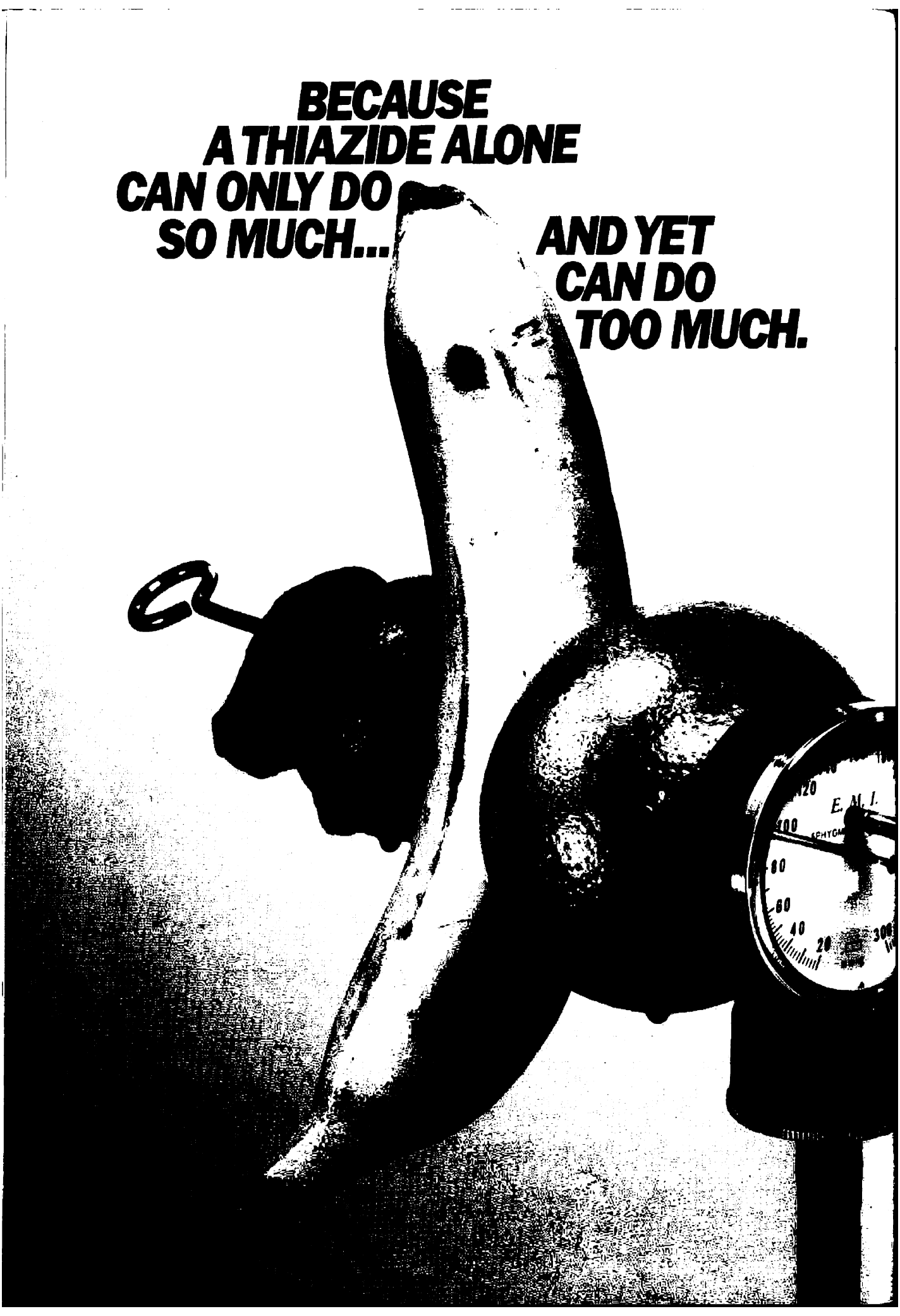

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A dependable means to long-term blood pressure control.

Many times, a diuretic alone can't keep hypertension in check. INDERIDE, however, can pick up where thiazide therapy leaves off.

The combination of propranolol HCl, the world's most trusted beta blocker, and hydrochlorothiazide, the standard among diuretics, enables INDERIDE to exert an additive antihypertensive effect.[1,2] In fact, a propranolol/hydrochlorothiazide regimen maintained blood pressure below 90 mm Hg in 81.8% to 86.4% of patients followed for 6 to 18 months of therapy.[1]

Low thiazide dosage means reduced risk of hypokalemia.

When thiazides are prescribed in doses greater than 50 mg/day, the potential for hypokalemia increases substantially. What's more, the greater the fall in serum K^+, the greater the risk of hypokalemia-induced PVCs.[3,4]

With INDERIDE, the additive hypotensive effect of propranolol HCl allows the effective dose of hydrochlorothiazide to be kept low (25 mg b.i.d.). And by lowering the daily dose of diuretic, INDERIDE also lowers the potential for diuretic-induced side effects. Potassium problems are less likely to occur—yet blood pressure can be controlled consistently.

INDERIDE

Each tablet contains INDERAL® (propranolol HCl) 40 mg or 80 mg and hydrochlorothiazide 25 mg

When you kno[illegible] than a

Please see Brief Summary of

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERIDE®

BRAND OF propranolol hydrochloride (INDERAL®) and hydrochlorothiazide

No. 474—Each INDERIDE®-40/25 tablet contains:
Propranolol hydrochloride (INDERAL®) . . . . . 40 mg
Hydrochlorothiazide . . . . . 25 mg
No. 476—Each INDERIDE®-80/25 tablet contains:
Propranolol hydrochloride (INDERAL®) . . . . . 80 mg
Hydrochlorothiazide . . . . . 25 mg

WARNING: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

DESCRIPTION: INDERIDE combines two antihypertensive agents: INDERAL (propranolol hydrochloride), a beta-adrenergic blocking agent, and hydrochlorothiazide, a thiazide diuretic-antihypertensive.

INDICATION: INDERIDE is indicated in the management of hypertension (See boxed warning.)

CONTRAINDICATIONS: Propranolol hydrochloride (INDERAL®): Propranolol hydrochloride is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with propranolol; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

Hydrochlorothiazide: Hydrochlorothiazide is contraindicated in patients with anuria or hypersensitivity to this or other sulfonamide-derived drugs.

WARNINGS: Propranolol hydrochloride (INDERAL®): CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. Propranolol acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by propranolol's negative inotropic effect. The effects of propranolol and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during propranolol therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of propranolol therapy. Therefore, when discontinuance of propranolol is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when propranolol is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long-term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since propranolol is a competitive inhibitor of beta-receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), propranolol should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. In patients with impaired renal function, cumulative effects of the drug may develop.

Thiazides should also be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Thiazides may add to or potentiate the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

USE IN PREGNANCY: Propranolol hydrochloride (INDERAL®): The safe use of propranolol in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

Hydrochlorothiazide: Thiazides cross the placental barrier and appear in cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers: Thiazides appear in breast milk. If the use of the drug is deemed essential, the patient should stop nursing.

PRECAUTIONS: Propranolol hydrochloride (INDERAL®): Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if propranolol is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of propranolol may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, namely: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause are: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or during concomitant use of corticosteroids or ACTH.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (*e.g.*, increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements such as foods with a high potassium content.

Any chloride deficit is generally mild, and usually does not require specific treatment except under extraordinary circumstances (as in liver or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Diabetes mellitus which has been latent may become manifest during thiazide administration.

Thiazide drugs may increase the responsiveness to tubocurarine.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration, have not been seen. Thiazides should be discontinued before carrying out tests for parathyroid function.

ADVERSE REACTIONS: Propranolol hydrochloride (INDERAL®): *Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Hydrochlorothiazide: *Gastrointestinal:* anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis.

Central Nervous System: dizziness, vertigo, paresthesias, headache, xanthopsia.

Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia.

Cardiovascular: orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Hypersensitivity: purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactio

Other: hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

DOSAGE AND ADMINISTRATION: The dosage must be determined by individual titration (see boxed warning).

Hydrochlorothiazide is usually given at a dose of 50 to 100 mg per day. The initial dose of propranolol is 40 mg twice daily and it may be increased gradually until optimum blood pressure control is achieved. The usual effective dose is 160 to 480 mg per day.

One to two INDERIDE tablets twice daily can be used to administer up to 320 mg of propranolol and 100 mg of hydrochlorothiazide. For doses of propranolol greater than 320 mg the combination products are not appropriate because their use would lead to an excessive dose of the thiazide component.

When necessary, another antihypertensive agent may be added gradually beginning with 50 percent of the usual recommended starting dose to avoid an excessive fall in blood pressure.

OVERDOSAGE OR EXAGGERATED RESPONSE: The propranolol hydrochloride (INDERAL) component may cause bradycardia, cardiac failure, hypotension, or bronchospasm.

The hydrochlorothiazide component can be expected to cause diuresis. Lethargy of varying degree may appear and may progress to coma within a few hours, with minimal depression of respiration and cardiovascular function, and in the absence of significant serum electrolyte changes or dehydration. The mechanism of central nervous system depression with thiazide overdosage is unknown. Gastrointestinal irritation and hypermotility can occur; temporary elevation of BUN has been reported, and serum electrolyte changes could occur, especially in patients with impairment of renal function.

TREATMENT: The following measures should be employed. GENERAL—If ingestion is, or may have been, recent, evacuate gastric contents taking care to prevent pulmonary aspiration. BRADYCARDIA—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. CARDIAC FAILURE—Digitalization and diuretics. HYPOTENSION—Vasopressors, *e.g.*, levarterenol or epinephrine. BRONCHOSPASM—Administer isoproterenol and aminophylline. STUPOR OR COMA—Administer supportive therapy as clinically warranted. GASTROINTESTINAL EFFECTS—Though usually of short duration, these may require symptomatic treatment. ABNORMALITIES IN BUN AND/OR SERUM ELECTROLYTES—Monitor serum electrolyte levels and renal function; institute supportive measures as required individually to maintain hydration, electrolyte balance, respiration, and cardiovascular-renal function.

HOW SUPPLIED: *No. 474*—Each INDERIDE®-40/25 tablet contains 40 mg propranolol hydrochloride (INDERAL®) and 25 mg hydrochlorothiazide, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 476—Each INDERIDE®-80/25 tablet contains 80 mg propranolol hydrochloride (INDERAL®) and 25 mg hydrochlorothiazide, in bottles of 100 and 1,000. Also in unit dose package of 100.

References: 1. Veterans Administration Cooperative Study Group on Antihypertensive Agents: J.A.M.A. 237:2303 (May 23) 1977. 2. Bravo, E.L., Terazi, R.C., and Dustan, H.P.: N. Engl. J. Med. 292:66 (Jan. 9) 1975. 3. Hollifield, J.W., and Slaton, P.E.: Acta Med. Scand. [Suppl.] 647:67, 1981. 4. Holland, O.B., Nixon, J.V. and Kuhnert, L.: Am. J. Med. 70:762 (Apr.) 1981.

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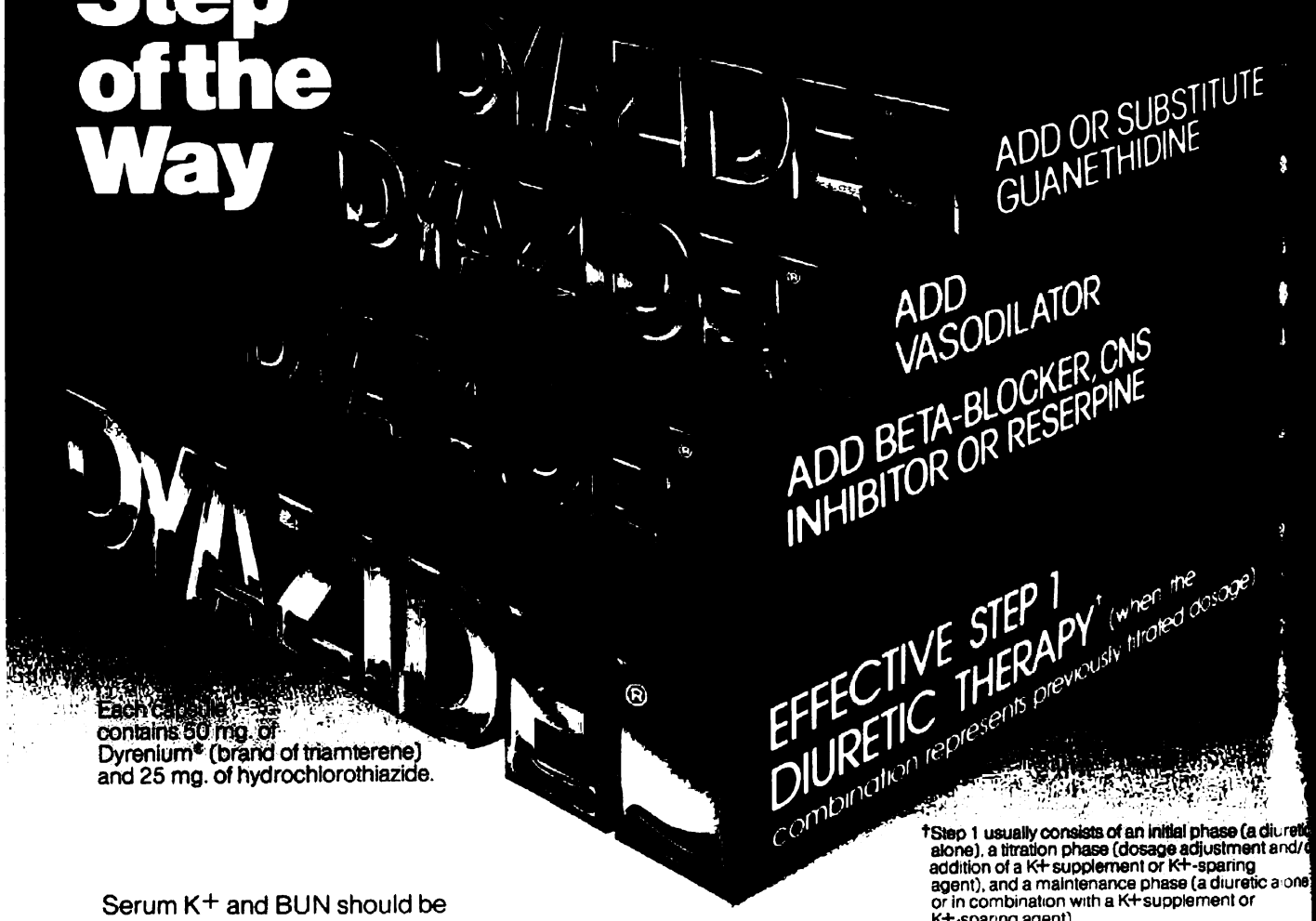
In Hypertension...When You Need to Conserve K

Every Step of the Way



Each capsule [illegible] contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K+ supplement or K+-sparing agent), and a maintenance phase (a diuretic alone or in combination with a K+ supplement or K+-sparing agent).

Serum K+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Watch for signs of impending coma in severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis and aplastic anemia have been reported with thiazides. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with Dyazide, but should it develop, corrective measures should be taken such as potassium supplementation, increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis and of impotence have been reported with the use of 'Dyazide' although a causal relationship has not been established.

Supplied: Bottles of 1000 capsules; Single Unit Package (unit-dose) of 100 (intended for institutional use only); Patient-Pak™ unit-of-use bottles of 100.

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THE NEVADA STATE MEDICAL ASSOCIATION PRESENTS

UPDATE: VASCULAR DISEASE 1982

SCIENTIFIC SESSION

Friday, May 14, 1982
MGM GRAND HOTEL, RENO

MGM GRAND HOTEL

CME Credits: Approved for AMA Category 1, AAFP and CE Units for Nurses.
Registration: 7:30 am - 8:00 am (coffee & rolls)

Welcome: Robert W. Clark, M.D., N.S.M.A. President
Program Chairman: Owen C. Peck, M.D.

8:00 am - 8:50 am **LARRY NOBLE, M.D.,** Asst. Professor of Internal Medicine, University of Nevada School of Medicine.
"NEWER DRUGS IN TREATMENT OF CARDIAC ARRHYTHMIAS"

8:50 am - 9:40 am **ROBERT S. ELIOT, M.D.,** Professor of Medicine, University of Nebraska School of Medicine;
"LIFESTYLE, BEHAVIOR AND STRESS IN CARDIOVASCULAR DISORDERS"

10:10 am - 11:00 am **JOHN E. CONTE, JR., M.D.,** Chief, Clinical and Infectious Disease, U.C. San Francisco School of Medicine.
"ENDOCARDITIS"

11:00 am - 11:50 am **GLENN A. LILLINGTON, M.D,** Chief, Pulmonary Disease, U.C. Davis Medical School.
"FIVE DISEASES CALLED PULMONARY EMBOLISM"

Noon - 2:00 pm Luncheon
Guest Speaker: **ROBERT S. ELIOT, M.D.**
"MANAGEMENT OF 20TH CENTURY STRESS"

2:00 pm - 2:50 pm **JERRY R. MAY, PH.D.,** Associate Professor of Psychiatry and Behavior Science, University of Nevada School of Medicine.
and
RALPH G. DePALMA, M.D., Chairman and Professor of Surgery, University of Nevada School of Medicine.
"SEX AND YOUR VASCULAR SYSTEM"

2:50 pm - 3:30 pm **NORMAN E. SHUMWAY, M.D., PH. D.,** Chairman, Department of Cardiovascular Surgery, Stanford Medical School.
"HEART TRANSPLANTATION AND HEART/LUNG TRANSPLANTATION"

REGISTRATION

PLEASE PRINT

Name _____

Address _____

City _____ State _____ Zip _____

Phone _____

SCIENTIFIC SESSION
FEES: Check one (includes luncheon)

NSMA Members	$100_____
Non-members	$125_____
Nurses	$ 50_____

Return to: Nevada State Medical Assn., 3660 Baker Ln., Reno, NV 89509. Or register by phone, (702) 825-6788, Kathy Nigro. Hotel reservation information will be forwarded upon receipt of your registration form.

96th ANNUAL MEETING

SANTA FE • MAY 5-7, 1982 • HILTON INN

WEDNESDAY, MAY 5 HOUSE OF DELEGATES, FIRST MEETING

2:00 pm **Convenes**—Guest Speaker: William Y. Rial, MD, President-elect, American Medical Association, Swarthmore, Pennsylvania

THURSDAY, MAY 6 SCIENTIFIC SESSION

8:00 am **Registration**

8:30 am **FIRST SESSION**—Presiding: Ashley Pond III, MD, President, New Mexico Medical Society
Risks and Benefits of Radiation

8:35 am **Overall View of Radiation in New Mexico** • Jonathan Mann, MD

9:00 am **Radiation Physics and Biology: What the Practitioner Needs to Know** • Louis Rosen, PhD

9:30 am **Low-Level Radiation: Facts and Facilities** • Edward Webster, PhD

10:15 am **BREAK**—VISIT EXHIBITS

10:45 am **Radiation During Pregnancy and Childhood** • Fred A. Mettler, Jr, MD

11:15 am **The Use of Office Radiology Equipment** • Edward Webster, PhD

12:00 noon **LUNCH BREAK**

2:00 pm **SECOND SESSION**—Presiding: Douglas Layman, MD, President-elect, New Mexico Medical Society

2:05 pm **Health Risks From Nuclear Fuel Cycle Activities in New Mexico** • George L. Voelz, MD

2:45 pm **Nuclear Waste Disposal in New Mexico: Medical Implications** • Jonathan Mann, MD

3:30 pm **BREAK**—VISIT EXHIBITS

4:00 pm **Medical Management of Radiation Accidents** • Fred A. Mettler, Jr, MD

4:30 pm **Panel—Perception of Medical Risks and Benefits**

R. C. Derbyshire, MD, Moderator
Douglas Layman, MD
Jonathan Mann, MD
Fred A. Mettler, Jr, MD
Louis Rosen, PhD
George Voelz, MD
Edward Webster, PhD

THURSDAY, MAY 6

6:30 pm **SPECIALTY SOCIETY MEETINGS—HILTON INN**
New Mexico Orthopaedic Association and New Mexico Chapter, Western Orthopaedic Association

Program: "The Cameroons"—John Moore, MD
"A Saudi Arabian Experience"—Charles Eberle, MD

NEW MEXICO MEDICAL SOCIETY

FRIDAY, MAY 7

8:00 am	**Registration**
8:30 am	**THIRD SESSION**—Presiding: William Liakos, MD, Vice-President, New Mexico Medical Society
8:35 am	**What's New and What Will It Cost?** • James Christie, MD
9:15 am	**Cats and Echoes—When to Order What?** • Jeffrey D. Wicks, MD
10:00 am	**BREAK**—VISIT EXHIBITS
10:30 am	**Concurrent Workshops**

Radiology—Trauma
Omar Legant, MD
William McPheron, MD

Radiology—Chest
William Ball, MD
James Stevenson, MD

Radiology—Abdominal
Larry Cohen, MD
Fred Hamilton III, MD

12:00 Noon **NEMPAC LUNCHEON**
Guest Speaker: Representative Joe Skeen

2:00 pm **House of Delegates, Second Meeting**

GUEST SPEAKERS, SCIENTIFIC SESSIONS

R. C. DERBYSHIRE, MD
Secretary-Treasurer, New Mexico State Board of Medical Examiners, Past President, New Mexico Medical Society, Santa Fe, New Mexico

JONATHAN MANN, MD
Assistant Director, Office of Health Promotion and Disease Prevention of the Health Services Division, New Mexico Department of Health and Environment, Santa Fe, New Mexico

LOUIS ROSEN, PhD
Division Leader, Meson Physics Division, Los Alamos National Laboratories, Los Alamos, New Mexico

OMAR LEGANT, MD
Private Practice—Radiology, Albuquerque, New Mexico

EDWARD WEBSTER, PhD
Professor of Radiology, Harvard Medical School, Chief, Radiological Sciences Division, Director of Radiation Safety, Massachusetts General Hospital, Boston, Massachusetts

FRED A. METTLER, JR, MD
Cancer Research and Treatment Center, Department of Diagnostic Imaging—President, New Mexico Society of Radiologists, Chapter of American College of Radiology, Albuquerque, New Mexico

GEORGE L. VOELZ, MD
Assistant Health Division Leader for Research and Development, Los Alamos National Laboratories, Los Alamos, New Mexico

JAMES H. CHRISTIE, MD
Faculty, Department of Radiology, University of New Mexico School of Medicine, Albuquerque, New Mexico

JEFFREY D. WICKS, MD
Faculty, Department of Radiology, University of New Mexico School of Medicine, Chief, Diagnostic Ultrasound—Cancer Research and Treatment Center, Albuquerque, New Mexico

WILLIAM McPHERON, MD
Private Practice—Radiology, Hobbs, New Mexico

WILLIAM BALL, MD
Faculty, Department of Radiology, University of New Mexico School of Medicine, Albuquerque, New Mexico

For Further Information or Registration Material

CONTACT: NEW MEXICO MEDICAL SOCIETY, 303 San Mateo, NE, Suite 204
Albuquerque, New Mexico 87108 • (505) 266-7868

Only Valium® (diazepam/Roche) is indicated in anxiety disorders and as an adjunct in the relief of skeletal muscle spasm

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy). The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

The clearance of Valium (diazepam/Roche) and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

How Supplied: For oral administration, Valium scored tablets—2 mg, white; 5 mg, yellow; 10 mg, blue—bottles of 100* and 500;* Prescription Paks of 50, available in trays of 10.* Tel-E-Dose* packages of 100, available in trays of 4 reverse-numbered boxes of 25,† and in boxes containing 10 strips of 10.†

*Supplied by Roche Products Inc., Manati, Puerto Rico 00701
†Supplied by Roche Laboratories, Division of Hoffmann-La Roche Inc., Nutley, New Jersey 07110

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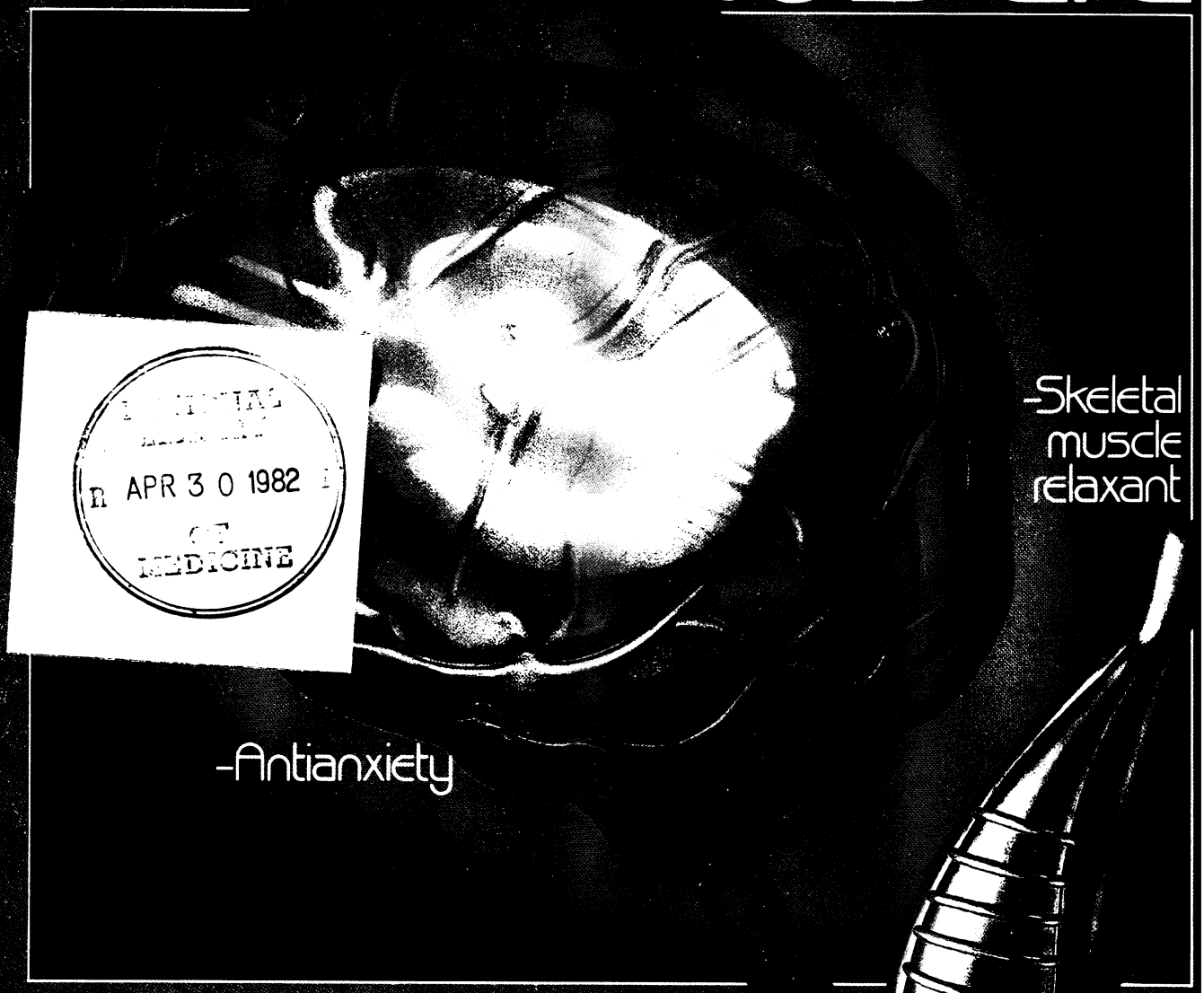

-Antianxiety

-Skeletal muscle relaxant

2-mg, 5-mg, 10-mg
• scored tablets

Valium® IV
diazepam/Roche

Indicated in anxiety disorders
and as an adjunct in the relief
of skeletal muscle spasm.

Please see summary
of product information
on preceding page.

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